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ITW

(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant:	AISSAOUI <i>et al.</i>	)	Confirmation No:	9192
		)		
Serial No.:	10/555,061	)	Group Art Unit:	1624
		)		
Filed:	October 28, 2005	)	Examiner:	Murray, Jeffrey H.
		)		
For:	QUINOXALIN-3-ONE DERIVATIVES AS	)	Docket No.:	AC-42-US
	OREXIN RECEPTOR ANTAGONISTS	)		

**MISCELLANEOUS COMMUNICATION**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

The Notice of Allowability was mailed on December 31, 2008, noting that claims 1-5 and 12 have been allowed. The examiner noted that acknowledgment is made of a claim for foreign priority, but the certified copy of the priority document has not been received. Therefore, Applicants enclosed herewith a certified copy of the foreign priority reference, PCT/EP03/04491.

The Examiner is invited to contact the undersigned by telephone in the event of any questions. As this response is filed within three months from the mailing date of the Notice of Allowability, which response is due March 31, 2009, this response is timely.

Respectfully submitted,

Dated: March 27, 2009

By   
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**CERTIFICATE UNDER 37 CFR 1.8:** The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as **EXPRESS MAIL**, Number: **E11275407306US**, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 27 day of March, 2009.

Patricia Mascenik  
Name

  
Signature

## Bescheinigung

Die angehefteten  
Unterlagen stimmen mit den  
in den Akten befindlichen  
Unterlagen der unten  
bezeichneten europäischen  
Patentanmeldung überein  
(Art.2 (3) des Beschlusses  
der Präsidentin des EPA  
vom 12.07.2007  
(Sonderausgabe Nr. 3, ABI.  
2007, J.2.)

## Certificate

The attached is a true copy  
of documents contained in  
the European patent  
application indicated below  
(Art.2(3) of the decision of  
the President of the EPO of  
12.07.2007 (Special edition  
No. 3, OJ EPO 2007, J.2.)

## Attestation

Les documents ci-annexés  
sont conformes aux  
documents figurant dans le  
dossier de la demande de  
brevet dont le numéro est  
indiqué ci-dessous (art.2(3)  
de la décision de la  
Présidente de l'OEB du  
12.07.2007 (Edition spéciale  
no. 3, JO OEB 2007, J.2.)

Patentanmeldung Nr.

Patent application No.

Demande de brevet n°

04729421.0



München, den  
Munich,

13.03.09

Die Präsidentin des Europäischen Patentamts:  
im Auftrag

For the President of the European Patent Office

La Présidente de l'Office européen des Brevets  
p.o.

Europäisches  
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### Bescheinigung

Die angehefteten Unterlagen  
stimmen mit der ursprünglich  
eingereichten Fassung der auf  
dem nächsten Blatt bezeichneten  
internationalen Patentanmeldung  
überein.

### Certificate

The attached documents  
are exact copies of  
the international patent  
application described on the  
following page, as originally  
filed

### Attestation

Les documents fixés à  
cette attestation sont  
conformes à la version  
initialement déposée de la  
demande de brevet internationale  
spécifiée à la page suivante.

Den Haag, den  
The Hague,  
La Haye, le

16.07.2007

Der Präsident des Europäischen Patentamts, i.A.  
For the President of the European Patent Office  
Le Président de l'Office européen des brevets, p.o.

TZIKAS Vangeli

Patentanmeldung Nr. PCT/EP2003/04491  
Patent application no.  
Demande de brevet n°





**Blatt 2 der Bescheinigung**  
**Sheet 2 of the certificate**  
**Page 2 de l'attestation**

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Anmeldenummer :  
Application no. : PCT/EP 2003/04491  
Demande n° :

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Bezeichnung der Erfindung :  
Title of the invention : NOVEL QUINOXALINONE DERIVATIVES  
Titre d'invention :

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Benennung von Vertragsstaaten : Siehe Formblatt PCT/RO/101 (beigefügt)  
Designation of contracting states : Sée Form PCT/RO/101 (enclosed)  
Désignation d'états contractants : Voir Formulaire PCT/RO/101 (ci-joint)

## PCT REQUEST

Actel 33/OR6

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IV-1	<b>Agent or common representative; or address for correspondence</b> The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	<b>agent</b>
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<b>V</b>	<b>Designation of States</b>	
V-1	<b>Regional Patent</b> (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	<b>AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&amp;LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT</b>
V-2	<b>National Patent</b> (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	<b>AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&amp;LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW</b>

ACTELION 33/OR6

### Novel Quinoxalinone Derivatives

5

The present invention relates to novel quinoxalinone derivatives of the general formula I and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula I, and especially their use as orexin receptor antagonists.

10

The orexins (hypocretins) comprise two neuropeptides produced in the hypothalamus: the orexin A (OX-A) (a 33 aminoacid peptide) and the orexin B (OX-B) (a 28 aminoacid peptide) (Sakurai T. *et al.*, *Cell*, 1998, 92, 573-585). Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behavior (Sakurai T. *et al.*, *Cell*, 1998, 92, 573-585). On the other hand, it was also proposed that orexins regulate states of sleep and wakefulness opening potentially novel therapeutic approaches for narcoleptic patients (Chemelli R.M. *et al.*, *Cell*, 1999, 98, 437-451). Two orexin receptors have been cloned and characterized in mammals. They belong to the superfamily of G-protein coupled receptors (Sakurai T. *et al.*, *Cell*, 1998, 92, 573-585): the orexin-1 receptor (OX<sub>1</sub>) is selective for OX-A and the orexin-2 receptor (OX<sub>2</sub>) is capable to bind OX-A as well as OX-B.

15

20

Orexin receptors are found in the mammalian host and may be responsible for many pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis; depressive neurosis; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; feeding disorders such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome/disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric diskinesia; gastric ulcer; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic

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hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed  
 5 biological and circadian rhythms; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal  
 10 failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions  
 15 associated with visceral pain such as irritable bowel syndrome, and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral  
 20 degeneration epilepsy; seizure disorders and other diseases related to orexin.

The present invention provides quinoxalinone derivatives which are non-peptide antagonists of human orexin receptors. In particular, these compounds are of potential use in the treatment of obesity and/or sleep disorders.

International Patent Applications WO099/09024, WO099/58533, WO00/47577,  
 25 WO00/47580, disclose phenyl urea derivatives and WO00/47576, discloses quinolinyl cinnamide derivatives as orexin antagonists.

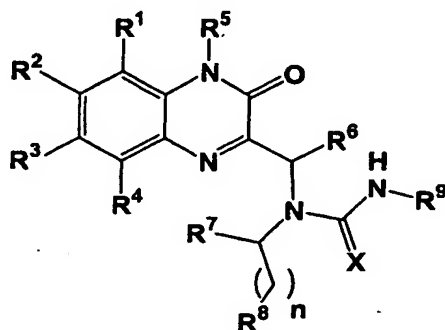
International Patent Applications WO 0251838 discloses tetrahydrobenzazepine derivatives and WO 0168609 discloses tetrahydroisoquinoline derivatives as orexin antagonists

30 Furthermore, WO 0196302 has been published wherein piperidine derivatives as OX<sub>1</sub> and OX<sub>2</sub> antagonists are disclosed and WO 0185693 has been published wherein N-acyltetrahydroisoquinoline derivatives as selective OX<sub>2</sub> antagonists are disclosed. In addition, WO 0244172 describes morpholine derivatives as antagonists of orexin

receptors. More recently, WO 0290355, WO 0289800, WO 0302559, WO 0302561 describe N-aryl cyclic amines as orexin antagonists and WO 0244172 describes morpholine derivatives as antagonists of orexin receptors.

5           The novel compounds of the present invention belong to an entirely different class of low molecular weight compounds as compared to all prior art orexin receptor antagonists so far published.

10           The present invention relates to novel quinoxalinone derivatives of the general formula (I).



Formula (I)

15

wherein:

X is O, S, NH, N-CN;

n is the integer 0, 1, 2, 3;

m is the integer 0, 1, 2, 3;

20   R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> independently represent cyano, nitro, halogen, hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclyl-lower alkyloxy, R<sup>10</sup>CO-, CO-NR<sup>11</sup>R<sup>12</sup>, R<sup>11</sup>R<sup>12</sup>N-, R<sup>10</sup>OOC-, R<sup>10</sup>SO<sub>2</sub>NH-, R<sup>13</sup>-CO-NH-, or R<sup>2</sup> and R<sup>3</sup> together or R<sup>1</sup> and R<sup>2</sup> together or R<sup>3</sup> and R<sup>4</sup> together

25   may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms which are separated by at least one carbon atom;

R<sup>5</sup> represents hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl, heterocyclyl-lower alkyl, trifluoromethyl, -(CH<sub>2</sub>)<sub>m</sub>-OH, -(CH<sub>2</sub>)<sub>m</sub>-

O-lower alkyl,  $-(CH_2)_m-CO_2H$ ,  $-(CH_2)_m-CO_2$ -lower alkyl,  $-(CH_2)_m-CONH_2$ , or  $-(CH_2)_m-CONH$ -lower alkyl;

$R^6$  represents hydrogen, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl, or heterocyclyl-lower alkyl;

5  $R^7$  represents hydrogen, aryl, lower alkyl, lower alkenyl, trifluoromethyl,  $-(CH_2)_m-OH$ ,  $-(CH_2)_m-O$ -lower alkyl,  $-(CH_2)_m-CO_2H$ ,  $-(CH_2)_m-CO_2$ -lower alkyl,  $-(CH_2)_m-CONH_2$ ,  $-(CH_2)_m-CONH$ -lower alkyl,  $-CON-(lower\ alkyl)_2$ ,  $-(CH_2)_m-N$ -lower alkyl;

$R^8$  represents aryl, aralkyl, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl, or heterocyclyl-lower alkyl;

10  $R^9$  represents aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl, or heterocyclyl-lower alkyl;

$R^{10}$  represents lower alkyl, aryl, aralkyl, heterocyclyl, or heterocyclyl-lower alkyl;

$R^{11}$  and  $R^{12}$  independently represent hydrogen, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, aralkyl, heterocyclyl, or heterocyclyl-lower alkyl;

15  $R^{13}$  represents lower alkyl, aryl, cycloalkyl, heterocyclyl,  $R^{11}R^{12}N-$ , or  $R^{10}O-$ .

The compounds of formula (I) can contain one or more asymmetric centres and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms  
20 and pharmaceutically acceptable salts thereof.

In the present description the term "lower alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1-5 carbon atoms. Examples of  
25 straight-chain and branched  $C_1-C_8$  alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isobutyl, tert-butyl, the isomeric pentylys, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, tert-butyl and n-pentyl.

30 The term "lower alkenyl", alone or in combination, signifies a straight-chain or branched-chain alkenyl group with 2 to 5 carbon atoms, preferably allyl and vinyl.

The term "lower alkoxy", alone or in combination, signifies a group of the

Formula lower-alkyl-O- in which the term "lower-alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy, preferably methoxy and ethoxy.

5 Lower alkenyloxy groups are preferably vinyloxy and allyloxy.

The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms.

Examples of C<sub>3</sub>-C<sub>8</sub> cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, preferably cyclopropyl, cyclohexyl or lower alkyl substituted  
10 cycloalkyl such as methyl-cyclopropyl, dimethyl-cyclopropyl, methyl-cyclobutyl, methyl-cyclopentyl, methyl-cyclohexyl, or dimethyl-cyclohexyl.

The term "aryl", alone or in combination, signifies a phenyl or naphthyl group which optionally carries one or more substituents, preferably one or two substituents, each independently selected from cyano, halogen, hydroxy, lower alkyl, lower alkenyl,  
15 lower alkoxy, lower alkenyloxy, nitro, trifluoromethyl, trifluoromethoxy, amino, carboxy, or alkoxycarbonyl such as phenyl, p-tolyl, 4-methoxyphenyl, 4-tert-butoxyphenyl, 4-fluorophenyl, 2-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl and 2-naphthyl. Preferred are carboxyphenyl, lower alkoxy-phenyl, hydroxyphenyl and particularly phenyl.

20 The term "aralkyl", alone or in combination, signifies a lower-alkyl or cycloalkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Preferred are benzyl and benzyl substituted in the phenyl ring with hydroxy, lower alkyl, lower alkoxy or halogen preferably fluorine. Particularly preferred is benzyl.

25 For the term "heterocyclyl" and "heterocyclyl-lower alkyl", the heterocyclyl group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated, partially unsaturated or aromatic containing for example 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur which may be the same or  
30 different. Examples of such heterocyclyl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, thienyl, thiazolyl, isothiazolyl, furyl, imidazolyl, pyrazolyl, pyrrolyl, indazolyl, indolyl, isoindolyl, isoxazolyl, oxazolyl, quinoxalinyl, phthalazinyl, cinnolinyl, dihydropyrrolyl, pyrrolidinyl, isobenzofuranyl, tetrahydrofuranyl,

dihydropyranyl. The heterocyclyl group may have up to 5, preferably 1, 2 or 3 optional substituents. Examples of suitable substituents include halogen, lower alkyl, amino, nitro, cyano, hydroxy, lower alkoxy, carboxy and lower alkyloxy-carbonyls.

5

The term "halogen" signifies fluorine, chlorine, bromine or iodine and preferably chlorine and fluorine and particularly fluorine.

10

The term "carboxy", alone or in combination, signifies a  $\text{-COOH}$  group.

Preferred compounds are compounds of the general formula I wherein  $n$  is the integer 0, 1 or 2,  $m$  is the integer of 0, 1 or 2,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  have the meaning given in the formula I above and  $X$  represents oxygen.

15 Examples of preferred compounds are:

3-(2-Ethoxy-phenyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-urea.

20 ((S)-1-phenyl-ethyl)-urea.

3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-((R)-1-phenyl-ethyl)-urea.

1-[1-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea.

25 3-Biphenyl-2-yl-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-urea.

3-(2-Ethoxy-phenyl-1-(2-methoxy-(S)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

30 3-(2-Ethoxy-phenyl-1-(2-methoxy-(R)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

*N*-Methyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.

*N*-Ethyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.

- N*-Cyclopropyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.
- (R)-2-{3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-ureido}-2-phenyl-acetamide.
- 5 (S)-2-{3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-ureido}-2-phenyl-acetamide.
- (3-{1-[3-(Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureido]-ethyl}-2-oxo-2*H*-quinoxalin-1-yl)-acetic acid ethyl ester.
- (2-Oxo-3-{1-[1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-ureido]-ethyl}-2*H*-quinoxalin-1-yl)-  
10 acetic acid ethylester.
- 2-{3-[3-(2-Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureidomethyl]-2-oxo-2*H*-quinoxalin-1-yl}-acetamide
- 1-Benzyl-3-(2-ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl-methyl)-urea.
- 15 1-Benzyl-3-(2-ethoxy-phenyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.
- 3-(2-Ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl-methyl)-1-(1-phenyl-ethyl)-urea.
- (S)-3-(2-Ethoxy-phenyl)-1-(3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-1-(1-phenyl-ethyl)-  
20 urea.
- 1-(6-Chloro-pyridin-3-ylmethyl)-3(2-ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-urea.
- (S)-3-(2-Ethoxy-phenyl)-1-(2-methoxy-1-phenyl-ethyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.
- 25 (R)-3-(2-Ethoxy-phenyl)-1-(2-methoxy-1-phenyl-ethyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.
- N*-(2-Ethoxy-phenyl)-*N'*-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-*N'*-1-phenyl-ethyl-cyanoguanidine.

30 Examples of physiologically usable or pharmaceutically acceptable salts of the compounds of formula (I) are salts with physiologically compatible mineral acids such as hydrochloric acid, sulphuric or phosphoric acid; or with organic acids such as methanesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The compounds of formula (I) with

free acidic groups can also form salts with physiologically compatible bases. Examples of such salts are alkali metal, alkali earth metal, ammonium and alkylammonium salts such as Na, K, Ca or tetraalkylammonium salt. The compounds of formula (I) can also be present in the form of a zwitterion.

5

Preferred compounds as described above have  $IC_{50}$  values below 100 nM; which have been determined with the FLIPR (Fluorometric Imaging Plates Reader) method described in the beginning of the experimental section.

10

The compounds of the general formula (I) and their pharmaceutically usable salts can be used for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as obesity, diabetes, prolactinoma, cardiovascular disorders, cancer, pain, narcolepsy, sleep disorders like insomnia, sleep apnea, parasomnia, depression, anxiety, addictions, schizophrenia, neurodegenerative disorders and dementia.

15

The compounds of formula (I) and their pharmaceutically usable salts are particularly useful for the treatment of obesity and sleep disorders.

20

The compounds of formula (I) may also be used in combination with one or more other therapeutically useful substances e.g. with other orexin receptor antagonists, with lipid lowering agents, with anorectic agents, with sleep inducing agents, with antidepressants or with other drugs beneficial for the prevention or treatment of obesity or sleep disorders.

25

The compounds of formula (I) and their pharmaceutically usable salts can be used as medicament (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered in enteral or oral form (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parenterally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

30

The compounds of formula (I) and their pharmaceutically usable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the

production of tablets, coated tablets, dragées, and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées, and hard gelatine capsules.

5            Suitable adjuvants for soft gelatine capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

            Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

10

            Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

            Suitable adjuvants for suppositories are, for example, natural or hardened oils,  
15        waxes, fats, semi-solid or liquid polyols, etc.

            Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or  
20        antioxidants. They can also contain still other therapeutically valuable substances.

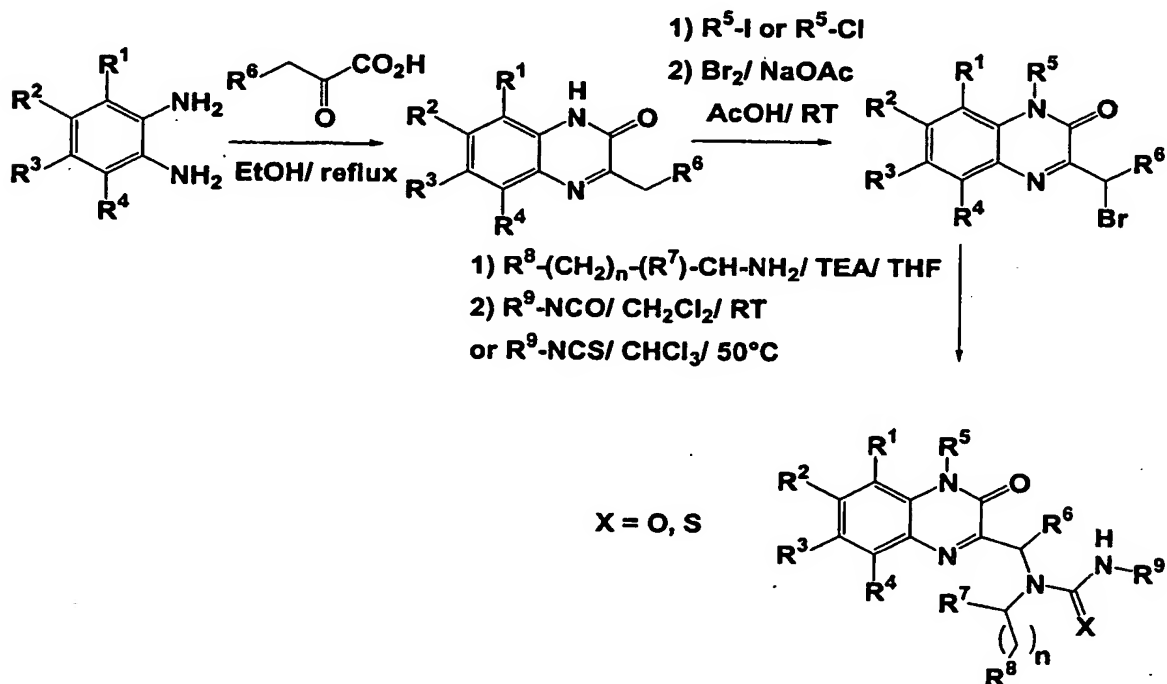
            The invention also relates to processes for the preparation of compounds of formula (I).

            The compounds of general formula (I) of the present invention are prepared  
25        according to the general sequence of reactions outlined in the schemes below, wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ , and  $R^9$  are as defined in formula (I) above. As the case may be any compound obtained with one or more optically active carbon atoms may be resolved into pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates and the meso-forms in a manner known per se.

30

            The compounds obtained may also be converted into a pharmaceutically acceptable salt thereof in a manner known per se.

As shown in Scheme 1, the compounds of general formula (I) may be prepared from the corresponding 1,2-phenylenediamine derivatives with the desired 2-oxo carboxylic acid at reflux in EtOH (Lawrence D. S. *et al.*, *J. Med. Chem.* 2001, 44, 4, 594-601; Bekerman D. G. *et al.*, *Journal of Heterocyclic Chem.* 1992, 29, 1, 129-133). Subsequent alkylation with  $R^5$ -I/ NaOH/ TBAB (Abdel-Ghany H. *et al.*, *Synthetic Communications*, 1990, 20, 6, 893-900) or with  $R^5$ -Cl/ NaOEt/ EtOH (Hermecz I. *et al.*, *Heterocycles* 1998, 48, 9, 1851-1866) followed by bromination leads to the corresponding bromo intermediate. A second alkylation with the corresponding primary amine yields the secondary amine which is then converted to the desired urea or thiourea compound by reaction with a commercially available or synthesized isocyanate or isothiocyanate (Scheme 1) (March J. *Advanced Organic Chemistry-Reactions, Mechanisms and Structure* 1992, page 418, 4<sup>th</sup> edition, John Wiley & Sons).

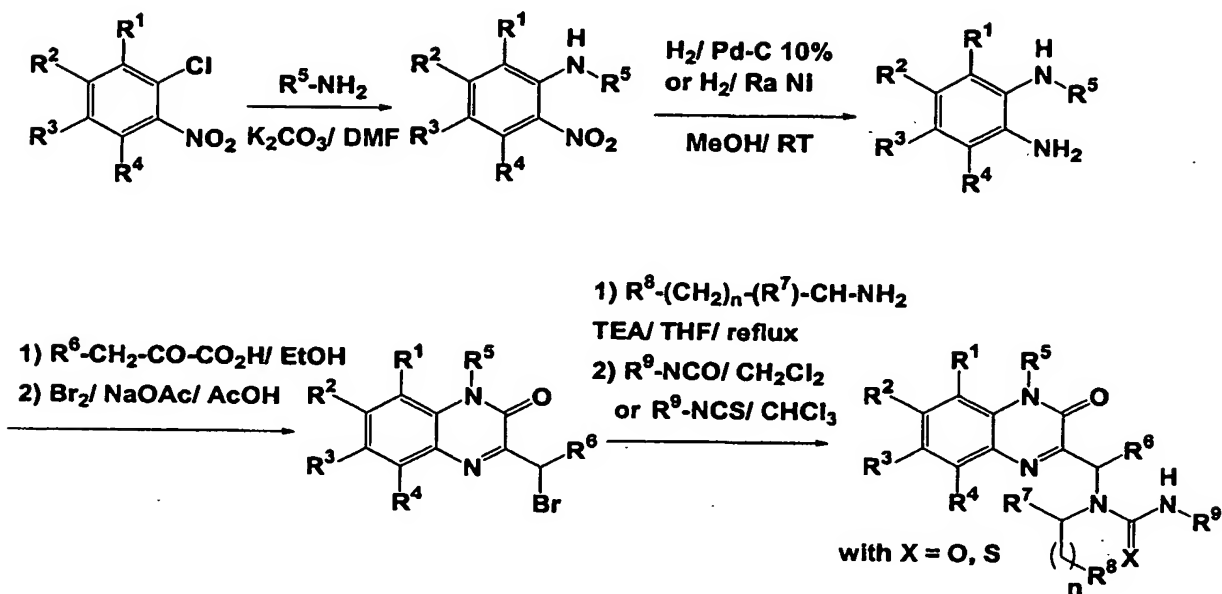


Scheme 1

The compounds of general formula (I) may be also prepared from the available 1-chloro-2-nitrobenzene derivative (Scheme 2). Amination under basic conditions followed by the hydrogenation of the resulting nitrobenzene derivative gives the desired aniline intermediate according to the method reported (see Obase H. *et al.*, *J. Heterocyclic Chem.* 1983, 20, 565-

573). This intermediate is then converted to the corresponding quinoxalinone derivative using the same conditions as described in Scheme 1.

5

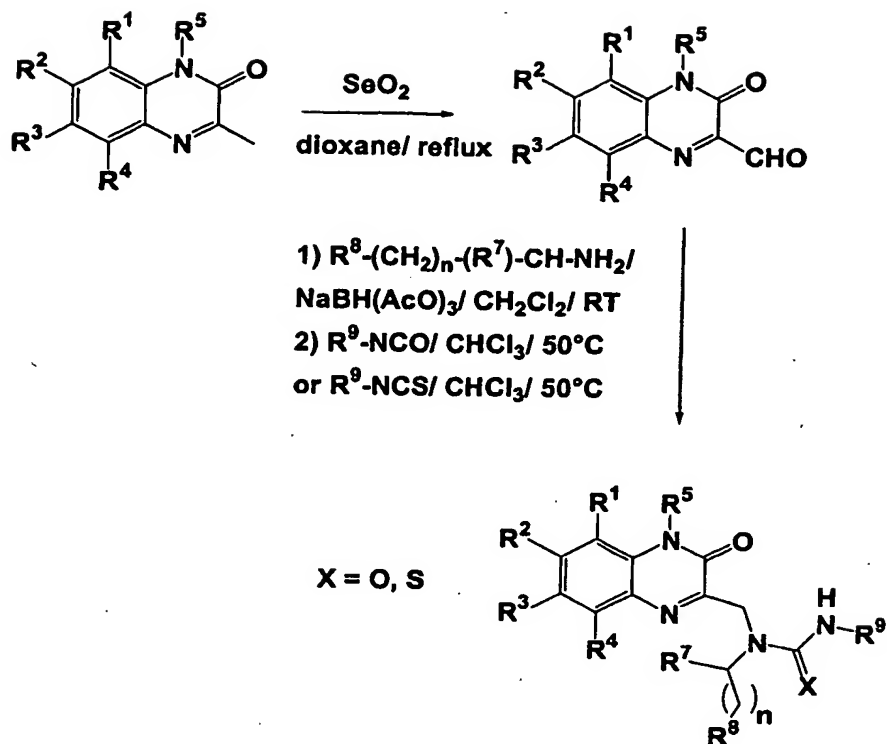


Scheme 2

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The compounds of general formula (I) wherein  $R^6$  is hydrogen may also be prepared by reductive amination of the 3-formyl-quinoxalin-2-one derivatives (synthesized by oxidation with selenium dioxide of the corresponding 3-methyl-quinoxalin-2-one derivative: see Ismail M.F. *et al.*, *Ind. J. Chem.* 1981, 20B, 5, 394-397 and Farghaly A.M. *et al.*, *Farmaco*, 1990, 45, 4, 431-438) with synthesized or commercially available primary amines (Scheme 3). The resulting secondary amine intermediate is then converted to the desired quinoxalinone derivative using the same conditions as described in Scheme 1.

15



Scheme 3

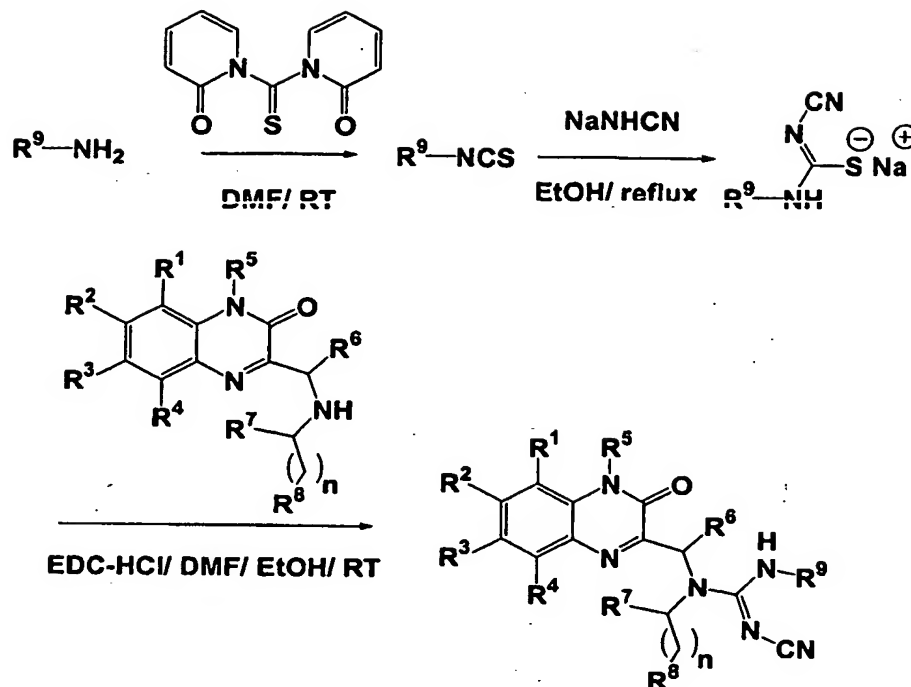
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The compounds of general formula (I) wherein  $\text{R}^9$  is aryl and X is N-CN (cyano-guanidine analogs) may be prepared from synthesized or commercially available isothiocyanate using known methods (see Poindexter G.S. *et al.*, WO 98/ 54136; Atwal K.S. *et al.*, *Tetrahedron Letters*, 1989, 30, 52, 7313-7316; Atwal K.S. *et al.*, *J. Med. Chem.* 1995, 38, 1966-1973) (Scheme 4).

10

15

20



Scheme 4

5

## Experimental Section

10

### I. Biology

#### Determination of $OX_1$ and $OX_2$ receptor antagonistic activities

The  $OX_1$  and  $OX_2$  receptor antagonistic activity of the compounds of formula (I) was determined in accordance with the following experimental method.

15

#### Experimental method:

##### Intracellular calcium measurements

20 Chinese hamster ovary (CHO) cells expressing the human orexin-1 receptor or the human orexin-2 receptor, were grown in culture medium (Ham F-12 with L-Glutamine) containing 300  $\mu\text{g/ml}$  G418, 100 U/ml penicillin, 100  $\mu\text{g/ml}$  streptomycin and 10 % inactivated foetal calf serum (FCS).

25 The cells were seeded at 80'000 cells / well into 96-well black clear bottom sterile plates (Costar) which had been precoated with 1% gelatine in Hanks' Balanced Salt Solution (HBSS). All reagents were from Gibco BRL.

The seeded plates were incubated overnight at 37°C in 5% CO<sub>2</sub>.

Human orexin-A as an agonist was prepared as 1 mM stock solution in methanol/ water (1:1), diluted in HBSS containing 0.1 % BSA and 2 mM HEPES for use in the assay at a final concentration of 10 nM.

- 5 Antagonists were prepared as 10 mM stock solution in DMSO, then diluted in 96-well plates, first in DMSO, then in HBSS containing 0.1 % bovine serum albumin (BSA) and 2 mM HEPES.

- 10 On the day of the assay, 100 µl of loading medium (HBSS containing 1% FCS, 2 mM HEPES, 5 mM probenecid (Sigma) and 3 µM of the fluorescent calcium indicator fluo-3 AM (1 mM stock solution in DMSO with 10% pluronic acid) (Molecular Probes) was added to each well.

The 96-well plates were incubated for 60 min at 37° C in 5% CO<sub>2</sub>. The loading solution was then aspirated and cells were washed 3 times with 200 µl HBSS containing 2.5 mM probenecid, 0.1% BSA, 2 mM HEPES. 100 µl of that same buffer was left in each well.

- 15 Within the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), antagonists were added to the plate in a volume of 50 µl, incubated for 20 min and finally 100 µl of agonist was added. Fluorescence was measured for each well at 1 second intervals, and the height of each fluorescence peak was compared to the height of the fluorescence peak induced by 10 nM orexin-A with buffer in place of antagonist. For each antagonist, IC<sub>50</sub> value (the concentration of compound needed to inhibit 50 % of the agonistic response) was determined. The IC<sub>50</sub> values of selected compounds are given in Table 1.
- 20

	<i>IC</i> <sub>50</sub> (nM)	
	<i>OX</i> <sub>1</sub>	<i>OX</i> <sub>2</sub>
Example 2	15	15
Example 3	15	11
Example 4	40	25
Example 6	5	2
Example 7	43	3
Example 8	53	23
Example 13	6	7
Example 14	14	9

*Table 1*

5

**II. Chemistry**

10 The following examples illustrate the preparation of pharmacologically active compounds of the invention but do not at all limit the scope thereof. All temperatures are stated in °C.

All hydrochloride salts were prepared by dissolving the free base in dichloromethane Followed by treatment with an excess of ethereal HCl (2M).

15

**A. Abbreviations**

20	AcOH	Acetic acid
	BSA	Bovine serum albumin
	CHO	Chinese hamster ovary
	DMAP	4-(Dimethylamino)pyridine
	DMF	Dimethylformamide

	DMSO	Dimethyl sulfoxide
	EDC-HCl	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	eq	equivalent
	ES	Electron spray
5	EtOH	Ethanol
	FC	Flash chromatography
	FCS	Foetal calf serum
	FLIPR	Fluorescent imaging plate reader
	HBSS	Hank's balanced salt solution
10	HEPES	4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid
	m	multiplet (NMR)
	MeCN	Acetonitrile
	MeOH	Methanol
	MS	Mass spectroscopy
15	NaOAc	Sodium acetate
	NMR	Nuclear magnetic resonance
	LC	Liquid chromatography
	q	quartet (NMR)
	Ra Ni	Raney nickel
20	R <sub>t</sub>	retention time
	rt	room temperature
	s	singlet (NMR)
	t	triplet (NMR)
	TBAB	n-Tetrabutylammonium bromide
25	TEA	Triethylamine
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran

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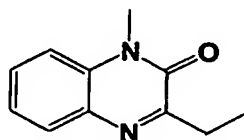
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## B. 1*H*-quinoxalin-2-one derivatives

### 1) General procedure:

- 5 A mixture of the 1,2-phenylene-diamine derivative (1 g) and the 2-oxo-carboxylic acid derivative (1 eq), in dry EtOH (35 mL) was stirred at reflux for 2 h under nitrogen. After cooling, the EtOH was evaporated to give a crude brown solid. Recrystallisation from EtOH gave the desired quinoxalin-2-one derivative.

#### 10 a) 3-Ethyl-1-methyl-1*H*-quinoxalin-2-one

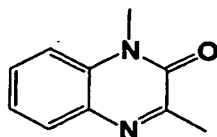


Reaction between *N*-methyl-1,2-phenylene-diamine and 2-oxo-butyric acid gave after recrystallisation (EtOH) 1.2 g (79%) of the title compound;

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): *R*<sub>t</sub> = 3.81 min. *m/z* = 189 (*M* + 1).

- 15 <sup>1</sup>H-NMR (300MHz; CDCl<sub>3</sub>) δ 1.35 (3H, t), 3.0 (2H, q), 3.7 (3H, s), 7.3 (2H, q), 7.5 (1H, t), 7.85 (1H, d).

#### b) 1,3-Dimethyl-1*H*-quinoxalin-2-one



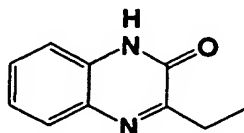
- 20 Reaction between *N*-methyl-1,2-phenylene-diamine and pyruvic acid gave after recrystallisation (EtOH) 1.2 g (84%) of the title compound;

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): *R*<sub>t</sub> = 3.26 min. *m/z* = 176 (*M* + 1).

<sup>1</sup>H-NMR (300MHz; CDCl<sub>3</sub>) δ 2.6 (3H, s), 3.7 (3H, s), 7.3 (2H, m), 7.55 (1H, t), 7.8 (1H, d).

25

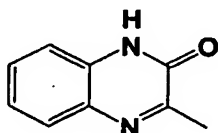
#### c) 3-Ethyl-1*H*-quinoxalin-2-one



Reaction between 1,2-phenylene-diamine and 2-oxo-butyric acid gave after recrystallisation (EtOH) 0.92 g (57%) of the title compound as a brown solid; LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 3.36 min. *m/z* = 175 (M + 1).

5 <sup>1</sup>H-NMR (300MHz; CDCl<sub>3</sub>) δ 2.4 (3H, t), 3.1 (2H, q), 7.3 (2H, t), 7.5 (1H, t), 7.85 (1H, d).

d) 3-Methyl-1*H*-quinoxalin-2-one

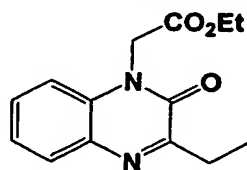


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Reaction between 1,2-phenylene-diamine and pyruvic acid gave after recrystallisation (EtOH) 0.65 g (73%) of the title compound as a beige solid; LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 2.91 min. *m/z* = 161 (M + 1).

15 <sup>1</sup>H-NMR (300MHz; DMSO-d<sub>6</sub>) δ 2.4 (3H, s), 7.25 (2H, t), 7.45 (1H, m), 7.85 (1H, d), 12.25 (1H, br.s).

e) (3-Ethyl-2-oxo-2*H*-quinoxalin-1-yl)-acetic acid ethylester



20

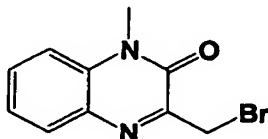
A mixture of 3-ethyl-1*H*-quinoxalin-2-one (1.6 g), ethyl chloroacetate (1.1 eq), NaOEt (1.1eq) in dry EtOH (15 mL) was stirred at reflux for 16 h under nitrogen. After cooling, the reaction mixture was evaporated in vacuo to dryness, and the residue was dissolved in ether. The resulting solution was washed with saturated NaHCO<sub>3</sub> solution, water, dried  
25 (anhydrous MgSO<sub>4</sub>), filtered and concentrated in vacuo to give a crude brown-orange solid.

FC (AcOEt/ heptane: 7/3) gave 1.4 g (43%) of the title compound as a brown solid. LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 2.91 min. *m/z* = 261 (M + 1).

$^1\text{H-NMR}$  (300MHz;  $\text{CDCl}_3$ )  $\delta$  1.35 (6H, tt), 3.00 (2H, q), 4.25 (2H, q), 5.00 (2H, s), 7.05 (1H, d), 7.35 (1H, t), 7.55 (1H, t), 7.85 (1H, d).

2) **3-Bromomethyl-1-methyl-1*H*-quinoxalin-2-one**

5



To a mixture of a 1,3-dimethyl-1*H*-quinoxalin-2-one (1g), anhydrous sodium acetate (0.565 g) in glacial AcOH (10 mL) was added dropwise over 10 min. a solution of bromine (0.295 mL) in glacial AcOH (6 mL). The resulting mixture was stirred at rt under nitrogen for 2h; then water and  $\text{CH}_2\text{Cl}_2$  was added successively. The aqueous layer was extracted once again with  $\text{CH}_2\text{Cl}_2$ , the combined organic extracts were dried (anhydrous  $\text{MgSO}_4$ ), filtered and concentrated to give a crude brown-orange residue.

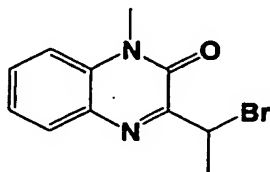
15 FC (AcOEt/ heptane: 1/1) gave 0.655 g (45%) of the title compound as a pink-orange solid.

LC-MS (MeCN/  $\text{H}_2\text{O}$ : 1/1):  $R_t$  = 3.91 min.  $m/z$  = 254 ( $M + 1$ ).

$^1\text{H-NMR}$  (300MHz;  $\text{CDCl}_3$ )  $\delta$  3.75 (3H, s), 4.7 (2H, s), 7.35 (2H, m), 7.6 (1H, m), 7.85 (1H, dd).

20

3) **3-(1-Bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one**



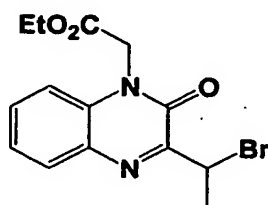
To a mixture of a 3-ethyl-1-methyl-1*H*-quinoxalin-2-one (1g) and anhydrous sodium acetate (0.523 g) in glacial AcOH (10 mL) was added dropwise over 10 min. a solution of bromine (0.273 mL) in glacial AcOH (6 mL). The resulting pale yellow suspension was stirred at rt under nitrogen for 2h, cooled to  $0^\circ\text{C}$ , filtered and washed with cold-water to give 1.05 g (73%) of the title compound as a pale yellow solid.

25

LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t$  = 3.91 min.  $m/z$  = 268 ( $M + 1$ ).

<sup>1</sup>H-NMR (300MHz; CDCl<sub>3</sub>)  $\delta$  2.1 (3H, t), 3.75 (3H, s), 5.7 (1H, m), 7.35 (2H, m), 7.6 (1H, m), 7.85 (1H, dd).

5 4) [3-(1-Bromo-ethyl)-2-oxo-2H-quinoxalin-1-yl] acetic acid ethyl ester

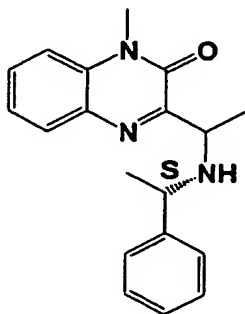


To a mixture of (3-methyl-2-oxo-2H-quinoxalin-1-yl)-acetic acid ethylester (1g), and anhydrous sodium acetate (0.38 g) in glacial AcOH (10 mL) was added dropwise over 10 min. a solution of bromine (0.2 mL) in glacial AcOH (6 mL). The resulting pale yellow suspension was stirred at rt under nitrogen for 2h, combined with water/ CH<sub>2</sub>Cl<sub>2</sub>, the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue. FC (AcOEt/ n-heptane: 1/1) gave 0.52 g (40%) of the title compound as a beige solid.

15 LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t$  = 2.91 min.  $m/z$  = 341 ( $M + 2$ ).

<sup>1</sup>H-NMR (300MHz; CDCl<sub>3</sub>)  $\delta$  1.25 (3H, t), 2.1 (3H, d), 4.25 (2H, q), 5.9 (1H, d), 6.2 (1H, d), 6.7 (1H, q), 7.1 (1H, d), 7.35 (1H, t), 7.55 (1H, t), 7.9 (1H, d).

20 5) 1-Methyl-3-[(R,S)-1-((S)-1-phenyl-ethylamino)-ethyl]-1H-quinoxalin-2-one

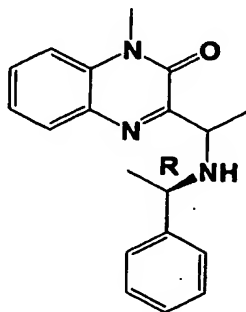


A mixture of rac-3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (S)-(-)- $\alpha$ -methylbenzyl amine (0.049 mL), and TEA (0.052 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was  
 5 combined with water/ CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue.

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) gave 0.1 g (86%) of the title compound as a brown-orange viscous oil.

10 LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): *R*<sub>t</sub> = 0.71 min. *m/z* = 308 (*M* + 1).

6) 1-Methyl-3-[(*R,S*)-1-((*R*)-1-phenyl-ethylamino)-ethyl]-1*H*-quinoxalin-2-one



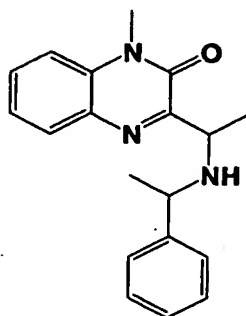
15 A mixture of rac-3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (*R*)-(+)- $\alpha$ -methylbenzyl amine (0.049 mL), and TEA (0.052 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was  
 20 combined with water/ CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue.

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) gave 0.09 g (75%) of the title compound as an orange viscous oil.

25 LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): *R*<sub>t</sub> = 0.71 min. *m/z* = 308 (*M* + 1).

7) 1-Methyl-3-[1-(1-phenyl-ethylamino)-ethyl]-1*H*-quinoxalin-2-one (mixture of diastereoisomers).

5



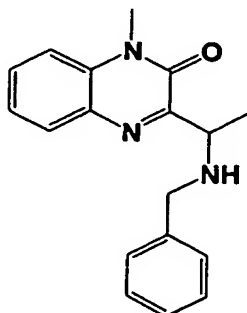
A mixture of rac-3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), DL (+/-)- $\alpha$ -methylbenzyl amine (0.049 mL), and TEA (0.052 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue.

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) gave 0.09 g (75%) of the title compound as an orange viscous oil.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> = 0.65 and 0.71 min.  $m/z$  = 308 (M + 1).

8) 3-(1-Benzylamino-ethyl)-1-methyl-1*H*-quinoxalin-2-one

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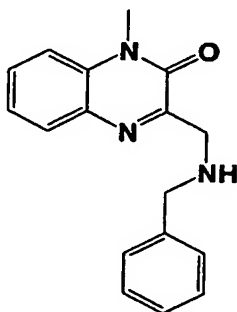


A mixture of 3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), benzylamine (0.041 mL), and TEA (0.052 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/  
 5 CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue.

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) gave 0.075 g (68%) of the title compound as an orange viscous oil.

10 LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): *R*<sub>t</sub> = 0.69 min. *m/z* = 294 (*M* + 1).

9) 3-(Benzylamino-methyl)-1-methyl-1*H*-quinoxalin-2-one

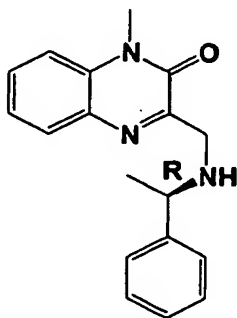


15 A mixture of 3-bromomethyl-1-methyl-1*H*-quinoxalin-2-one (0.1 g), benzylamine (0.043 mL), and TEA (0.055 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH<sub>2</sub>Cl<sub>2</sub>,  
 20 and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue.

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) gave 0.095 g (86%) of the title compound as an orange viscous oil.

25 LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): *R*<sub>t</sub> = 0.71 min. *m/z* = 280 (*M* + 1).

10) **[R]-1-methyl-3-[(1-phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one**



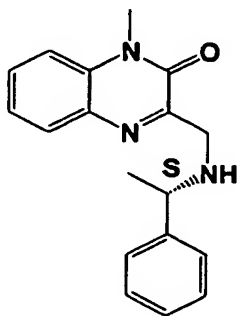
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A mixture of 3-bromomethyl-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (R)-(+)- $\alpha$ -methylbenzyl amine (0.05 mL), and TEA (0.055 mL) in dry THF (1 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was  
 10 combined with water/CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue.

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) gave 0.095 g (82%) of the title compound as an orange viscous oil.

15 LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> = 0.69 min. *m/z* = 294 (M + 1).

11) **[S]-1-methyl-3-[(1-phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one**



20

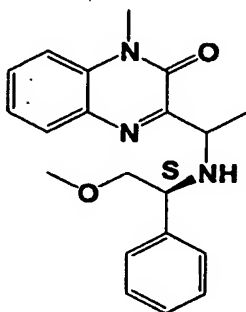
A mixture of 3-bromomethyl-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (S)-(+)- $\alpha$ -methylbenzyl amine (0.05 mL), and TEA (0.055 mL) in dry THF (1 mL) was stirred at

reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue.

- 5 FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) gave 0.085 g (73%) of the title compound as an orange viscous oil.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> = 0.69 min. *m/z* = 294 (M + 1).

- 10 12) 3-[(R,S)-1-(2-Methoxy-(S)-1-phenyl-ethylamino)-ethyl]-1-methyl-1*H*-quinoxalin-2-one

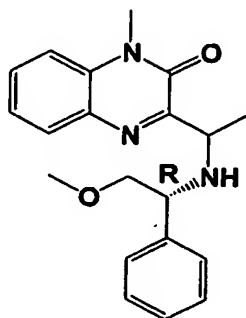


- 15 A mixture of rac-3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (S)-(+)-1-amino-1-phenyl-2-methoxyethane (57 mg, 1eq), and TEA (0.055 mL) in dry THF (2.5 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue.

- 20 FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) gave 0.060 g (47 %) of the title compound as a brown- orange viscous oil.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> 2.98 min. *m/z* = 338 (M + 1).

13) 3-[(R,S)-1-(2-Methoxy-(R)-1-phenyl-ethylamino)-ethyl]-1-methyl-1*H*-quinoxalin-2-one



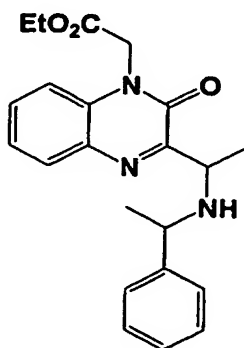
5

A mixture of rac-3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (R)-(-)-1-amino-1-phenyl-2-methoxyethane (57 mg, 1eq), and TEA (0.055 mL) in dry THF (2.5 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue.

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) gave 0.086 g (68 %) of the title compound as a brown- orange viscous oil.

15 LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> 2.98 min. *m/z* = 338 (M + 1).

14) {2-Oxo-3-[1-(phenyl-ethylamino)-ethyl]-2*H*-quinoxalin-1-yl}-acetic acid ethylester (mixture of diastereoisomers) acid



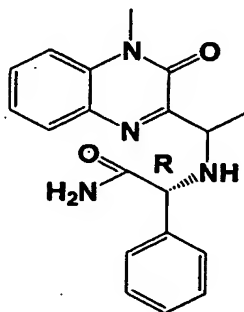
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A mixture of [3-(1-bromo-ethyl)-2-oxo-2*H*-quinoxalin-1-yl] acetic acid ethyl ester (0.1 g), (D,L)-(+/-)- $\alpha$ -methylbenzylamine (35.8 mg, 1eq), and TEA (0.041 mL) in dry THF (2.5 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue.

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) gave 0.076 g (68 %) of the title compound as a brown- orange viscous oil.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> 0.76 min.  $m/z$  = 380 (M + 1).

**15) (R)-2-[(R,S)-1-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethylamino]-2-phenyl-acetamide**

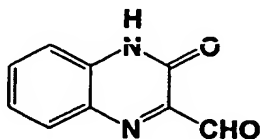


A mixture of 3-(1-bromo-ethyl)-1-methyl-1*H*-quinoxalin-2-one (0.1 g), (R)-(-)-2-phenylglycine amide (57 mg, 1eq), and TEA (0.055 mL) in dry THF (2.5 mL) was stirred at reflux for 20 h under inert atmosphere. After cooling to rt, the reaction mixture was combined with water/ CH<sub>2</sub>Cl<sub>2</sub>, and the aqueous layer was extracted once again with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude brown-orange residue.

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/1) gave 0.109 g (87 %) of the title compound as a pale brown viscous oil.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> 2.70 min.  $m/z$  = 338 (M + 2).

16) 3-Oxo-3,4-dihydro-quinoxaline-2-carbaldehyde

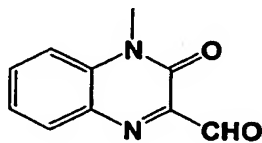


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A mixture of 3-methyl-1*H*-quinoxalin-2-one (0.5 g) and selenium dioxide (0.728 g, 2.1 eq) in dry dioxane (33 mL) was stirred at reflux under nitrogen for 30 min. After cooling, the dark-brown mixture was concentrated under reduced pressure and the residue was purified by FC (AcOEt) to give 0.44 g (81%) of the title compound as an orange solid.

<sup>1</sup>H-NMR (300MHz; DMSO-*d*<sub>6</sub>)  $\delta$  7.35 (2H, q), 7.7 (1H, t), 7.9 (1H, d), 10.2 (1H, s), 12.8 (1H, br.s).

17) 4-Methyl-3-oxo-3,4-dihydro-quinoxaline-2-carbaldehyde



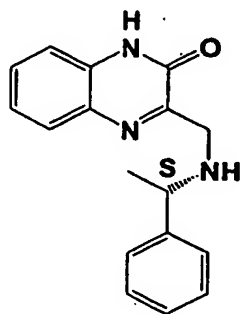
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A mixture of 1,3-dimethyl-1*H*-quinoxalin-2-one (1 g) and selenium dioxide (1.33 g, 2.1 eq) in dry dioxane (60 mL) was stirred at reflux under nitrogen for 30 min. After cooling, the dark-brown mixture was concentrated under reduced pressure and the residue was purified by FC (AcOEt) to give 0.997 g (92%) of the title compound as a yellow solid.

<sup>1</sup>H-NMR (300MHz; DMSO-*d*<sub>6</sub>)  $\delta$  3.8 (3H, s), 7.35-7.45 (2H, m), 7.7 (1H, t), 8.1 (1H, d), 10.5 (1H, s).

30

18) [S]-3-[(1-Phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one



5

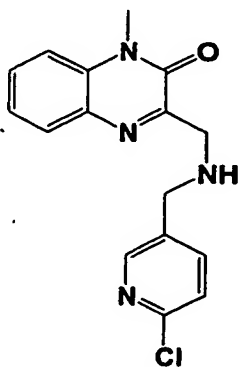
A mixture of 3-oxo-3,4-dihydro-quinoxaline-2-carbaldehyde (0.1 g), sodium triacetoxyborohydride (0.182 g, 1.5 eq), and (S)-(+)- $\alpha$ -methylbenzyl amine (70 mg) in dry  $\text{CH}_2\text{Cl}_2$  (1.2 mL) was stirred at rt under nitrogen for 1 day. After cooling, the dark-brown mixture was concentrated under reduced pressure and the residue was purified by FC (AcOEt) to give 0.28 g (18%) of the title compound as an orange solid.

10

LC-MS (MeCN/  $\text{H}_2\text{O}$ : 1/1 + 0.04% TFA):  $R_t$  = 0.66 min.  $m/z$  = 280 ( $M + 1$ ).

19) 3-[[[6-Chloro-pyridin-3-ylmethyl)-amino]]-1-methyl-1*H*-quinoxalin-2-one

15



A mixture of 4-methyl-3-oxo-3,4-dihydro-quinoxaline-2-carbaldehyde (0.1 g), sodium triacetoxyborohydride (0.170 g, 1.5 eq), and 2-chloro-5-aminomethylpyridine (0.076 g, 1eq) in dry  $\text{CH}_2\text{Cl}_2$  (1.5 mL) was stirred at rt under nitrogen for 1 day. After cooling, the dark-brown mixture was concentrated under reduced pressure and the residue was purified

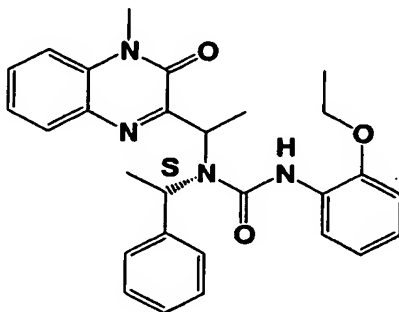
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by FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/ 1) to give 0.086 g (51%) of the title compound as an orange oil.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 2.93 min. *m/z* = 315 (M + 1).

## 5 Example 1

**3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-(S)- phenyl-ethyl)-urea**



10

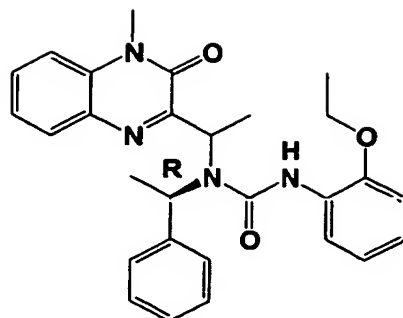
To a solution of 1- Methyl-3-[(R,S)-1-((S)-1-phenyl-ethylamino)-ethyl]-1*H*-quinoxalin-2-one (50 mg, 0.163 mmol) in dry CHCl<sub>3</sub> (1 mL), was added 2-ethoxyphenyl isocyanate (26.3 mg, 0.163 mmol). The resulting reaction mixture was stirred at 50°C under nitrogen for 20h. The reaction mixture was then concentrated under reduced pressure and the residue was purified by FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 19/ 1) to give the title compound as a yellow foam (45%).

15

LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> = 1.03 min. *m/z* = 471 (M + 1).

## 20 Example 2

**3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-((R)-1-phenyl-ethyl)-urea**

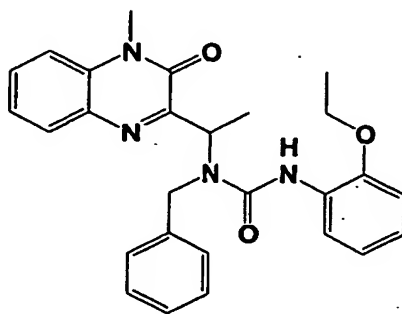


In analogy to Example 1 using the 1- Methyl-3-[(R,S)-1-((R)-1-phenyl-ethylamino)-ethyl]-1H-quinoxalin-2-one (1 eq).

- 5 FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 19/ 1) afforded the title compound as a yellow oil (48%).  
LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> = 1.03 min. *m/z* = 471 (M + 1).

### Example 3

- 10 **(R,S)-1-Benzyl-3-(2-ethoxy-phenyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea**



15

In analogy to Example 1 using the 3-(1-benzylamino-ethyl)-1-methyl-1H-quinoxalin-2-one (1 eq).

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 19/ 1) afforded the title compound as a brown-orange oil (43%).  
LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> = 1.01 min. *m/z* = 457 (M + 1).

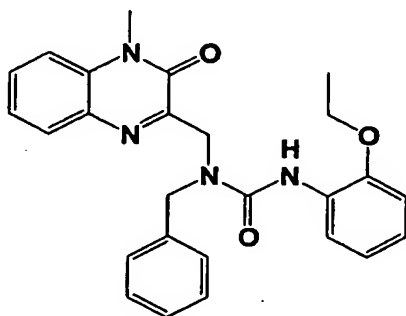
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25

**Example 4**

5

**1-Benzyl-3-(2-ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-urea**



10

In analogy to Example 1 using the 3-(benzylamino-methyl)-1-methyl-1*H*-quinoxalin-2-one (1 eq).

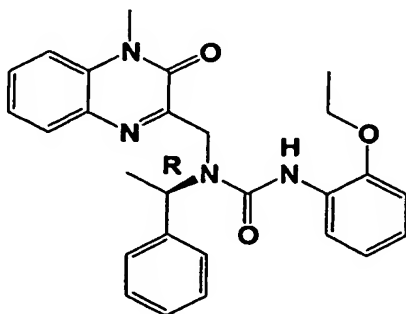
FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 19/ 1) afforded the title compound as an orange oil (57%).

15 LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> = 0.98 min. *m/z* = 443 (M + 1).

**Example 5**

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**[R]-3-(2-Ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-1-(phenyl-ethyl)-urea**



25

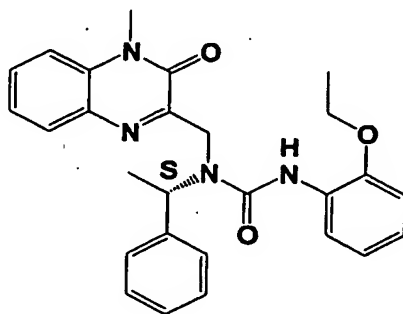
In analogy to Example 1 using the [R]-1-methyl-3-[(1-phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one (1 eq).

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 19/ 1) afforded the title compound as an orange oil (57%).

5 LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> = 1.00 min. *m/z* = 457 (M + 1).

### Example 6

10 [S]-3-(2-Ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-1-(phenyl-ethyl)-urea



15 In analogy to Example 1 using the [S]-1-methyl-3-[(1-phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one (1 eq).

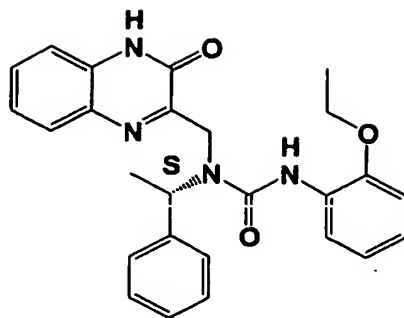
FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 19/ 1) afforded the title compound as an orange oil (32%).

LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04%): R<sub>t</sub> = 1.00 min. *m/z* = 457 (M + 1).

### Example 7

20

[S]-3-(2-Ethoxy-phenyl)-1-(3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-1-(1-phenyl-ethyl)-urea



- 5 In analogy to Example 1 using the [S]-3-[(1-phenyl-ethylamino)-methyl]-1*H*-quinoxalin-2-one (1 eq)

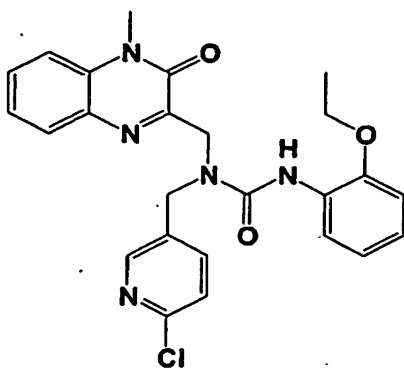
FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/ 1) afforded the title compound as a pale-yellow solid (72%).

LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> = 0.94 min. *m/z* = 443 (M + 1).

10 **Example 8**

**1-(6-Chloro-pyridin-3-ylmethyl)-3(2-ethoxy-phenyl)-1(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-urea.**

15



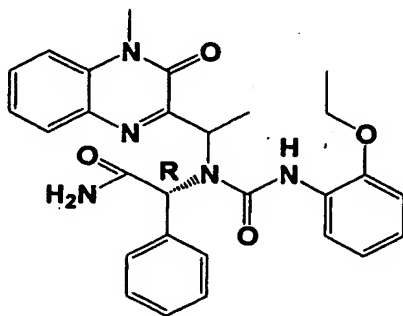
- 20 In analogy to Example 1 using the 3-{{{(6-chloro-pyridin-3-ylmethyl)-amino}}}-1-methyl-1*H*-quinoxalin-2-one (1eq)

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/ 1) afforded the title compound as a yellow foam (50%).

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 4.86 and 5.41 min. *m/z* = 478 (M + 1).

### Example 9

- 5 **[R]-2-{3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-ureido}-2-phenyl-acetamide.**



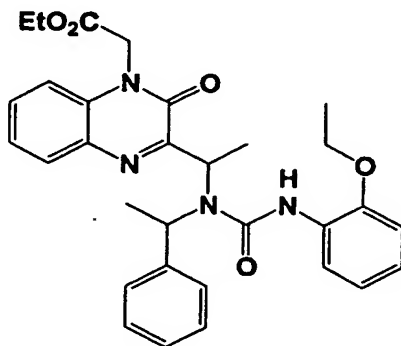
- 10 In analogy to Example 1 using the [R]-2-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethylamino]-2-phenyl-acetamide (1eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as white foam (32%).

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 4.63 min. *m/z* = 500 (M + 1).

### 15 Example 10

**(3-{1-[3-(Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureido]-ethyl}-2-oxo-2*H*-quinoxalin-1-yl)-acetic acid ethyl ester (mixture of diastereoisomers)**



In analogy to Example 1 using the {2-Oxo-3-[1-(phenyl-ethylamino)-ethyl]-2H-quinoxalin-1-yl}-acetic acid ethylester (1eq).

FC (AcOEt/ heptane: 3/ 7) afforded the title compound as an orange oil (79%).

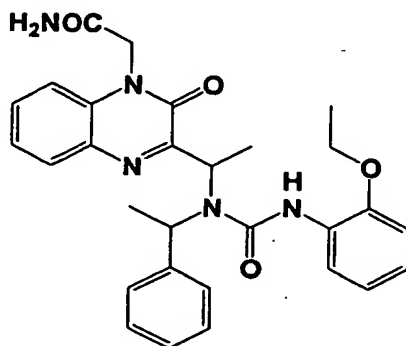
LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> = 0.95 min. *m/z* = 543 (M + 1).

5

### Example 11

2-{3-[3-(2-Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureido]-ethyl}-2-oxo-2H-quinoxalin-1-yl}-acetamide (mixture of diastereoisomers)

10



A mixture of (3-{1-[3-(2-Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureido]-ethyl}-2-oxo-2H-quinoxalin-1-yl)-acetic acid ethyl ester (0.11 g), and aqueous NaOH 2N (0.5 mL, 5 eq) in a mixture MeOH/ dioxane (4/3) (1.7 mL) was stirred at rt for 20 h. Then the reaction mixture was combined with water/ AcOEt, the aqueous phase was acidified until pH 1-2 with aqueous HCl 2N, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (three times). The combined organic extracts were dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated in vacuo to give the crude acid as a white foam (0.09 g, 85%). To this crude acid (0.05 g) in dry CH<sub>2</sub>Cl<sub>2</sub> (1.4 mL), were added successively EDC-HCl (0.026 g, 1eq), DMAP (0.035 g, 3eq), and NH<sub>3</sub> 0.5 N in dioxane (0.20 mL, 1eq); the resulting mixture was stirred at rt under nitrogen for 20 h. The mixture was then combined with CH<sub>2</sub>Cl<sub>2</sub>/ aqueous HCl 2N. The organic layer was washed twice with water, dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated in vacuo to give a crude oil.

FC (CH<sub>2</sub>Cl<sub>2</sub>/ MeOH: 9/ 1) afforded the title compound as a beige foam (100%).

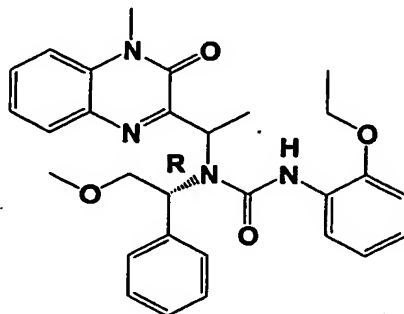
LC-MS (MeCN/ H<sub>2</sub>O: 1/1 + 0.04% TFA): R<sub>t</sub> = 0.91 min. *m/z* = 514 (M + 1).

25

**Example 12**

**3-(2-Ethoxy-phenyl)-1-(2-methoxy-(R)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.**

5



In analogy to Example 1 using the 3-[(R,S)-1-(2-Methoxy-(R)-1-phenyl-ethylamino)-ethyl]-1-methyl-1*H*-quinoxalin-2-one (1eq).

10

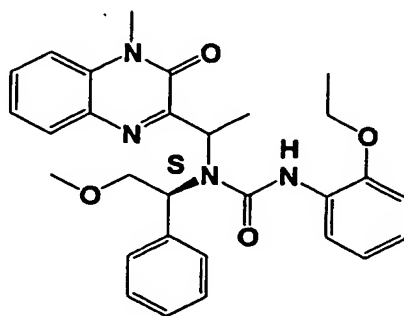
FC (AcOEt/ heptane: 1/1) afforded the title compound as a pale brown oil (25%).

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 5.27 min. *m/z* = 501 (M + 1).

**Example 13**

15

**3-(2-Ethoxy-phenyl)-1-(2-methoxy-(S)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.**



20

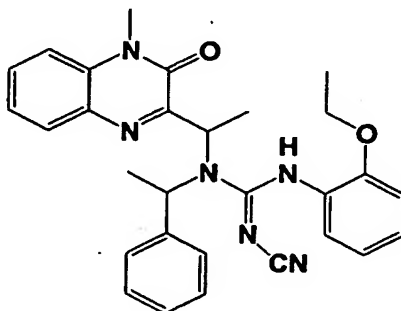
In analogy to Example 1 using the 3-[(R,S)-1-(2-Methoxy-(S)-1-phenyl-ethylamino)-ethyl]-1-methyl-1*H*-quinoxalin-2-one (1eq).

FC (AcOEt/ heptane: 1/1) afforded the title compound as a pale brown oil (52%).

- 5 LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t = 5.28$  min.  $m/z = 501$  (M + 1).

#### Example 14

- 10 *N*-(2-Ethoxy-phenyl)-*N*-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-cyanoguanidine (mixture of diastereoisomers)



15

A mixture of 2-ethoxyphenyl isothiocyanate (0.1 g) and sodium hydrogencyanamide (35.71 mg, 1eq) in dry EtOH (2 mL) was stirred at reflux under nitrogen for 3 h. After cooling to rt, EDC-HCl (0.107 g, 1eq) and a solution of 1-methyl-3-[1-(1-phenyl-ethylamino)-ethyl]-1*H*-quinoxalin-2-one (0.172 g, 1eq) in dry DMF (1 mL) were added and the resulting mixture reaction was stirred at rt under nitrogen for 20 hours. The mixture was then combined with AcOEt and sat. NaHCO<sub>3</sub>, the aqueous layer was extracted once again with AcOEt. The combined organic extracts were washed with brine, dried (anhydrous MgSO<sub>4</sub>), filtered and concentrated to give a crude pale-brown oil.

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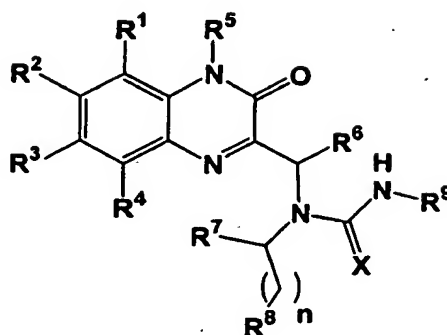
FC (AcOEt/ n-heptane: 7/3) gave the title compound as a white solid (0.051 g, 18%).

25

LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t = 5.26$  min.  $m/z = 495$  (M).

## Claims

### 1. Compounds of the general formula (I)



Formula (I)

wherein:

X is O, S, NH, N-CN;

n is the integer 0, 1, 2, 3;

m is the integer 0, 1, 2, 3;

$R^1, R^2, R^3, R^4$  independently represent cyano, nitro, halogen, hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclyl-lower alkyloxy,  $R^{10}CO-$ ,  $-CO-NR^{11}R^{12}$ ,  $R^{11}R^{12}N-$ ,  $R^{10}OOC-$ ,  $R^{10}SO_2NH-$ ,  $R^{13}-CO-NH-$ , or  $R^2$  and  $R^3$  together or  $R^1$  and  $R^2$  together or  $R^3$  and  $R^4$  together may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms which are separated by at least one carbon atom;

$R^5$  represents hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl, heterocyclyl-lower alkyl, trifluoromethyl,  $-(CH_2)_m-OH$ ,  $-(CH_2)_m-O$ -lower alkyl,  $-(CH_2)_m-CO_2H$ ,  $-(CH_2)_m-CO_2$ -lower alkyl,  $-(CH_2)_m-CONH_2$ ,  $-(CH_2)_m-CONH$ -lower alkyl;

$R^6$  represents hydrogen, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^7$  represents hydrogen, aryl, lower alkyl, lower alkenyl, trifluoromethyl,  $-(CH_2)_m-OH$ ,

$-(CH_2)_m-O$ -lower alkyl,  $-(CH_2)_m-CO_2H$ ,  $-(CH_2)_m-CO_2$ -lower alkyl,  $-(CH_2)_m-CONH_2$ ,  
 $-(CH_2)_m-CONH$ -lower alkyl,  $-CON$ -(lower alkyl)<sub>2</sub>,  $-(CH_2)_m-N$ -lower alkyl;

$R^8$  represents aryl, aralkyl, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

5  $R^9$  represents aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^{10}$  represents lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^{11}$  and  $R^{12}$  independently represent hydrogen, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

10  $R^{13}$  represents lower alkyl, aryl, cycloalkyl, heterocyclyl,  $R^{11}R^{12}N$ - or  $R^{10}O$ -

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

2. Compounds of the general formula I, wherein n is the integer 1 or 2, m is the integer 1 or 2,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^7$  have the meaning given in the formula I above and X represents oxygen.

3. Compounds of the general formula I wherein n is the integer 1 or 2, m is the integer 1 or 2,  $R^5$  represents methyl,  $R^6$  represents phenyl,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , and  $R^7$  have the meaning given in the formula I above and X represents oxygen.

20 4. A compound according to any one of claims 1 to 3, selected from the group consisting of 3-(2-Ethoxy-phenyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-urea.

3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-((S)-1-phenyl-ethyl)-urea.

25 3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-((R)-1-phenyl-ethyl)-urea.

1-[1-(4-Methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea.

30 3-Biphenyl-2-yl-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-1-(1-phenyl-ethyl)-urea.

3-(2-Ethoxy-phenyl)-1-(2-methoxy-(S)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

- 3-(2-Ethoxy-phenyl)-1-(2-methoxy-(R)-1-phenyl-ethyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.
- N*-Methyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.
- 5 *N*-Ethyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.
- N*-Cyclopropyl-2-[3-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-3-(1-phenyl-ethyl)-ureido]-benzamide.
- (R)-2-{3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-ureido}-2-phenyl-acetamide.
- 10 (S)-2-{3-(2-Ethoxy-phenyl)-1-[(R,S)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-ureido}-2-phenyl-acetamide.
- (3-{1-[3-(Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureido]-ethyl}-2-oxo-2*H*-quinoxalin-1-yl)-acetic acid ethyl ester.
- 15 (2-Oxo-3-{1-[1-(1-phenyl-ethyl)-3-(2-*n*-propyl-phenyl)-ureido]-ethyl}-2*H*-quinoxalin-1-yl)-acetic acid ethylester.
- 2-{3-[3-(2-Ethoxy-phenyl)-1-(1-phenyl-ethyl)-ureidomethyl]-2-oxo-2*H*-quinoxalin-1-yl}-acetamide
- 1-Benzyl-3-(2-ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl-methyl)-urea.
- 20 1-Benzyl-3-(2-ethoxy-phenyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.
- 3-(2-Ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl-methyl)-1-(1-phenyl-ethyl)-urea.
- 25 (S)-3-(2-Ethoxy-phenyl)-1-(3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-1-(1-phenyl-ethyl)-urea.
- 1-(6-Chloro-pyridin-3-ylmethyl)-3(2-ethoxy-phenyl)-1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-ylmethyl)-urea.
- (S)-3-(2-Ethoxy-phenyl)-1-(2-methoxy-1-phenyl-ethyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.
- 30 (R)-3-(2-Ethoxy-phenyl)-1-(2-methoxy-1-phenyl-ethyl)-1-[1-(4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-urea.

*N*-(2-Ethoxy-phenyl)-*N*'-[1-(-4-methyl-3-oxo-3,4-dihydro-quinoxalin-2-yl)-ethyl]-*N*'-1-phenyl-ethyl-cyanoguanidine.

5. Pharmaceutical compositions for the treatment of disorders which are associated with the role of orexin, comprising obesity and sleep disorders, cardiovascular disorders, cancer, pain, depression, schizophrenia or neurodegenerative disorders, containing one or more compounds of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, and usual carrier materials and adjuvants.
6. The compounds of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use as medicaments for the treatment of disorders which are associated with a role of orexin, comprising obesity, sleep disorders, cardiovascular disorders, cancer, pain, depression, schizophrenia or neurodegenerative disorders.
7. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound as claimed in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof.
8. A process for the manufacture of pharmaceutical compositions for the treatment of disorders associated with the role of orexin, obesity, sleep disorders, cardiovascular disorders, cancer, pain, depression, schizophrenia or neurodegenerative disorders, containing one or more compounds as claimed in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, as active ingredients which process comprises mixing one or more active ingredient or ingredients with pharmaceutically acceptable excipients and adjuvants in a manner known per se.
9. Use of one or more compounds of any one of claims 1 to 4 in combination with other pharmacologically active compounds comprising other orexin receptor antagonists, lipid lowering agents, anorectic agents, sleep inducing agents, antidepressants or other drugs beneficial for the prevention or treatment of disorders given in any one of claims 5 to 8.
10. A compound as described as end-product in any one of examples 1 to 23.

**Abstract**

The invention relates to novel quinoxalinone derivatives and their use as active ingredients  
5 in the preparation of pharmaceutical compositions. The invention also concerns related  
aspects including processes for the preparation of the compounds, pharmaceutical  
compositions containing one or more of those compounds and especially their use as  
orexin receptor antagonists.

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